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A hitchhiker's guide through the COVID-19 galaxy

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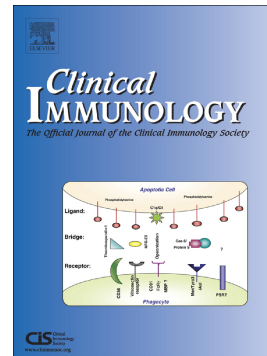
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Title: **A hitchhiker's guide through the COVID-19 Galaxy**

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Abstract: Numerous reviews have summarized the epidemiology, pathophysiology and the various therapeutic aspects of Coronavirus disease 2019 (COVID-19), but a practical guide on "how to treat whom with what and when" based on an understanding of the immunological background of the disease stages remains missing.

This review attempts to combine the current knowledge about the immunopathology of COVID-19 with published evidence of available and emerging treatment options.

We recognize that the information about COVID-19 and its treatment is rapidly changing, but hope that this guide offers those on the frontline of this pandemic an understanding of the host response in COVID-19 patients and supports their ongoing efforts to select the best treatments tailored to their patient's clinical status.

Figure 1.
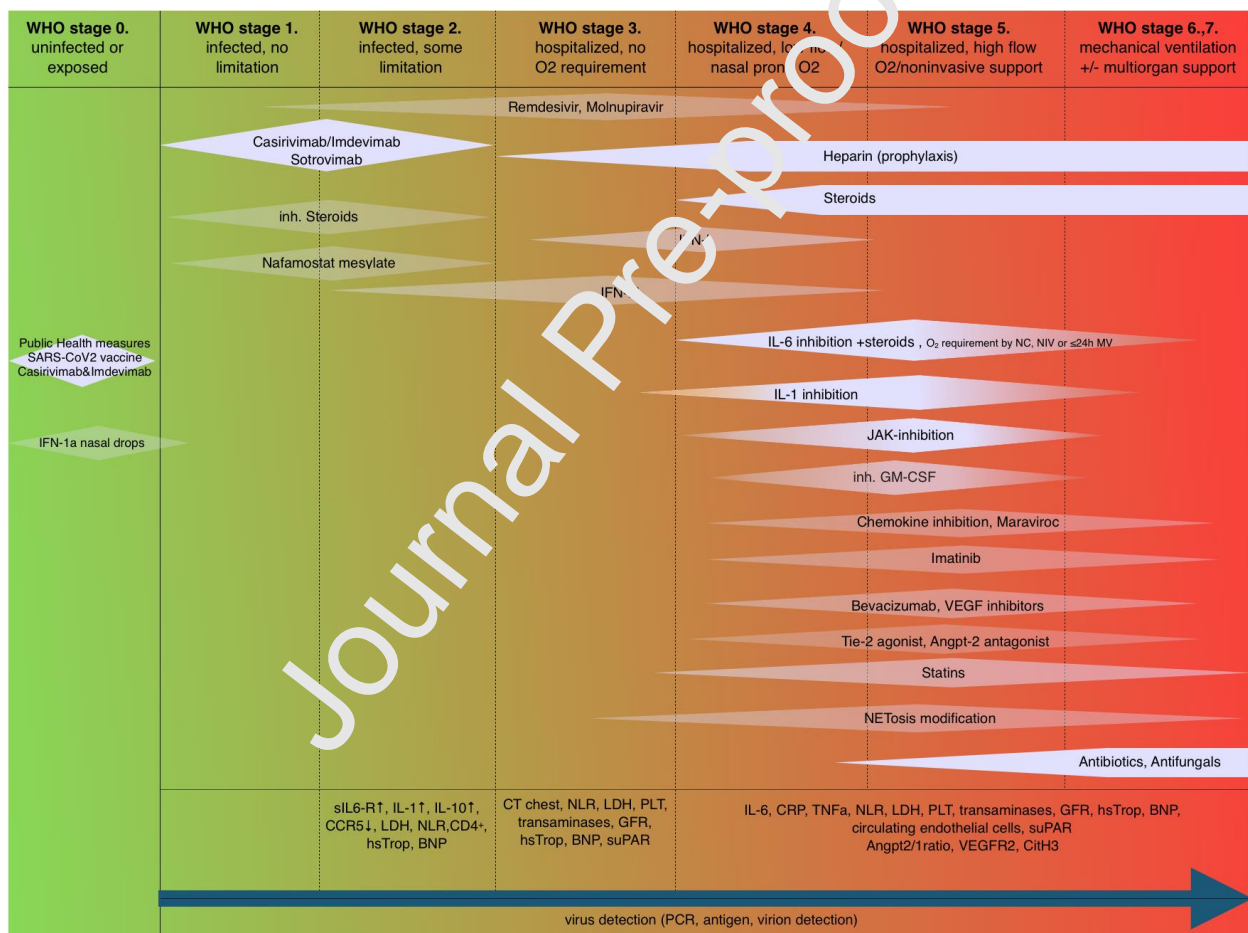
Introduction

Since SARS-CoV-2 was first identified in December 2019 in Wuhan, China [1], coronavirus disease 2019 (COVID-19) has evolved into a pandemic resulting in 223 million infections and almost 4.6 million deaths [2]. Due to the rapid global spread of the virus and lack of adequate worldwide vaccine coverage, novel viral variants differing in transmission dynamics and pathogenicity have continued to evolve and now dominate among patients requiring hospitalization [3, 4]. After exposure to the virus, typically through aerosol or droplet particles, SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE2) receptor, enriched on the surfaces respiratory [5-9] and intestinal epithelia [9]. Expression of ACE-2 on endothelium remains controversial, but some data supports that endothelial infection takes place [10-12].

The incubation period averages 3 (2-14) days [13-15], subject to host factors [16-21] and viral variant involved [22]. A recent metanalysis of 350 studies found that approximately a third of infected individuals remain asymptomatic [23] but can still shed virus and transmit the disease [24-27]. Most who do develop symptoms experience a mild disease course that may include fever, cough, myalgia, diarrhea, sore throat, and a loss of smell and taste [28, 29]. However, since the emergence of new variants and more rigorous testing, there has been a shift in the hospitalization risk. Between November 2020 and January 2021, the absolute risk of hospitalization overall was 4.7% in individuals testing positive for the alpha variant, reaching 21.4% in those over 80 years of age [30]. A more recent study, including over 43.000 SARS-CoV-2 positive individuals, approximately half of whom were asymptomatic, found a hospitalization rate of 2.3% following infection with the delta variant, which after adjustment, is twice the hospitalization risk when compared to the alpha variant [31].

Of those hospitalized, 20-30% [32] progress to acute respiratory distress syndrome (ARDS), which remains the leading cause of death. Among the 4.3% 2.5% of hospitalized patients [32-36], one to two-thirds of those requiring intensive care [37-39], and as many as 75% with COVID-19-associated ARDS may not survive [33].

Changes in patient management have had a significant impact on outcomes. Inpatient mortality reportedly decreased from 26% [40-42] at the beginning of 2020 to 7.6% [41] by mid-2020. Notably, much of this development is owed to improved outcomes in hospitalized patients who never progressed to mechanical ventilation (MV), whereby there has been little change in the prognosis of those with severe disease [36].

Vaccinations have reduced the risk of severe disease even more significantly. Recent CDC data showed that the risk of infection and hospitalization were 4.9 and 29.2 times lower in vaccinated when compared to unvaccinated individuals, respectively. When hospitalization did occur, progression to severe disease was significantly less likely in vaccinated patients[43].

The reported overall case fatality ranges from 0.4%-1%[30, 44], with individual risk determined by a relatively well-defined set of parameters [45, 46]. Patients at highest risk for disease progression are [47-53]:

- unvaccinated
- male
- of older age
- have comorbidities including obesity (BMI$\geq$30kg/m^2), hypertension, diabetes
- have other chronic pre-existing conditions involving the cardiovascular, respiratory or renal systems

Moderate to severe COVID-19 is characterized by a dysregulated immune response resulting in a multisystem process dominated by endothelial activation and a prothrombotic state [54-56] and involving the cardiovascular, hepatic, renal and neurological systems [57-61]. The multisystem nature of the vascular involvement has been illustrated on whole body or lung PET-CTs of COVID-19 patients [62] and may even persist in survivors experiencing ongoing symptoms [63].

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Therefore, a thorough understanding of the immunopathology in COVID-19 is critical for selecting the most appropriate therapeutic interventions and preventing patient exposure to unnecessary or potentially harmful treatments.

The **key immunologic processes of COVID-19** include:

- an initial rapid increase in viral load
- excessive and prolonged innate immune activation
- epi-and endothelial barrier dysfunction
- a pro-coagulant state
- excessive pulmonary neutrophil recruitment and formation of neutrophil extracellular traps (NETs)

These processes are also implicated in other infectious and inflammatory conditions. It remains to be determined if and to what extent the immune mechanisms observed in COVID-19 indeed differ from infectious and non-infectious conditions such as SIRS, inflammatory ARDS, and other systemic hyperinflammatory states.

To classify disease severity and assist in standardizing of research protocols, the **WHO** has developed an **ordinal 9 point scale** (Figure 1) reflecting the various stages of disease progression [64, 65]. Applying this scale, this article attempts to match the underlying immunopathology of COVID-19 with evidence-based treatment modalities published in the peer-reviewed literature. We recognize that during the progression of the disease to severe COVID-19, these processes overlap, influence one another, and are causally linked. As the clinical picture evolves, different processes emerge and therapeutic targets change. Our knowledge of the immunopathology and therapeutic options in COVID-19 is expanding daily. Best up to date advice will be found online through resources, such as the regularly revised websites of the NIH and WHO.

1. WHO 9 point Scale, Patient Stage 0. No clinical or virological evidence of infection

Until vaccines achieve protection at a population level, social distancing, face masks, and hand hygiene are effective and necessary measures mitigating infection risk [66].

Over 114 vaccine candidates utilizing a diverse set of technologies are currently in clinical development[67]. Vaccination with mRNA constructs targeting influenza, rabies, zika or chikungunya virus have been subject to research efforts for some time and are now applied to SARS-CoV-2 [68-70]. Of those, two mRNA based vaccines, mRNA1273 from Moderna, Tozinameran from the BioNTech/Pfizer partnership and two adenovirus-vector vaccines, AZD1222 from AstraZeneca and the single-dose Janssen/Johnson & Johnson vaccine, have been granted Emergency Use Authorization (EUA) as COVID-19 vaccines in the US since December 2020.

In addition, an adjuvanted inactivated virus vaccine by Sinovac and the heterologous recombinant adenovirus vaccine Sputnik V have been in widespread use.

Vaccines provide high-level protection from SARS-CoV-2 infection and severe disease and elicit a robust antibody and B- and T- cell response [71, 72]. However, despite the effective initial humoral vaccine response, neutralization activity declines over time. To what extent serum antibody titers are a proxy for reinfection risk remains to be determined, but evidence for neutralizing activity and protection from (re)infection is emerging[73].

A recent large study demonstrated that antibody titers in response to the two most widely used mRNA vaccines decreased significantly after six months [74]. In addition, vaccine-induced efficacy against emerging viral variants is reduced [75, 76], supporting recent discussions for the need for booster vaccines.

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In summary, the observation of breakthrough infections in vaccinated people, decreasing antibody titers following vaccination and emergence of new escape variants all highlight the ongoing need for close surveillance of this highly dynamic situation.

Based on published evidence, therapeutic recommendations include

Since vaccines have become available, other prophylactic measures have become less relevant. However, they may remain of importance for select high-risk individuals, especially when suboptimal vaccine responses may be expected, such as in the immunocompromised.

1. Vaccines
as discussed above

2. Casirivimab and Imdevimab
The use of the monoclonal antibody combination casirivimab plus imdevimab (see below) as post-exposure prophylaxis has been shown to result in a significant reduction of symptomatic SARS-CoV-2 infections compared with placebo (1.5% vs 7.8%; OR 0.17; $p<0.001$) [77]. As a result of these findings, the Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for this combination as post-exposure prophylaxis within seven days [78].

3. Topical Interferon-1α
Type 1 Interferon is critically involved in the early antiviral response [79, 80] (see below). Prophylactic use of IFN-1α nasal drops four times daily in 3000 uninfected health care workers (HCWs) resulted in no symptomatic SARS-CoV-2 infections in any of the patient-facing staff [81]. Controlled studies investigating the role of IFN-1α in preventing COVID-19 are underway (NCT04552379, NCT04320238) [82].

> **Take home messages for this stage:**
> 1. Social distancing, wearing face masks, eye protection and hand hygiene are effective measures mitigating an infection risk
> 2. Vaccination is the primary prophylactic measure. Until final data analysis of future phase III/IV trials are available, the duration of protection from clinical disease will remain undetermined.
> 3. Combination treatment of casirivimab and imdevimab is effective postexposure prophylaxis
> 4. Other prophylactic measures such as IFN-1α and monoclonal antibody preparations might be of value in certain high risk groups

2. WHO 9 point Scale, Patient Stage 1. Infection, Ambulatory, no limitation of activities

During the incubation period, patients are asymptomatic, and many will never develop symptoms as described above. In others, epithelial infection and local inflammation may result in symptoms consistent with a mild viral infection [83].
As in most the disease does not progress further, the critical question here is if treatment is required at all and, if so, for whom.
High-risk patients should be monitored closely to initiate therapeutic interventions at the first signs of disease progression.
SARS-CoV-2 replication peaks early, *at symptom onset*, so the timing of virostatic therapies is critical. Delayed antiviral treatment may shorten viral shedding but not significantly affect the viral load (VL) [84]. Outpatients with a higher VL one week after symptom onset are more likely to be hospitalized and prolonged shedding of replication-competent virus is associated with more severe disease [21, 85, 86]. This suggests that early antiviral treatment may curb the rapid early replication and possibly influence the risk of disease progression.

Based on published evidence about this disease stage, therapeutic recommendations include

1. Antiviral therapy:
Nucleotide analogs - remdesivir, favipiravir, galidesivir and others [87] - mainly act by inhibiting the viral RNA-dependent RNA polymerase and thereby viral replication.

a. **Remdesivir** (RDV) is an adenosine analogue initially developed as a treatment against Ebolavirus [88-91]. It is administered intravenously (iv.) as oral bioavailability is poor. Lipid analogues [92] and dry powder preparations for inhalation [93] addressing this shortcoming are under development. Treatment duration in trials range from 5 to 10 days, dosed at 200 mg OD on day one followed by 100mg. The primary dose-limiting effect is hepatotoxicity, and monitoring of liver function and coagulation is recommended.
Key trials assessing RDV use in COVID-19 [94] have limited enrolment to hospitalized patients. In ACTT-1 (Adaptive COVID-19 Treatment Trial), a double-blinded and placebo-controlled trial [95], RDV accelerated clinical recovery (10d vs 15d, p<0.001) and reduced 28 day mortality, driven by patients at WHO stage 4 (HR 0.30 [0.14-0.64]) [95]. In SIMPLE-1 [96], five days of RDV in addition to standard of care was associated with clinical improvement at day 11 in hospitalized patients, mainly at WHO stage 3 (OR 1.65; [1.09-2.48], p=0.02) [96, 97].
In the much larger WHO-led Solidarity trial (11,266 hospitalized patients of varying severity), RDV did not impact 28 day mortality (HR 0.95; [0.81-1.11] overall, HR 0.86; [0.67-1.11] not ventilated, HR 1.2; [0.80-1.80] ventilated), progression to MV or length of hospital stay. This included patients without oxygen requirement WHO stage 3, as well as 4ff [98].
As a result of the above, the WHO no longer recommends RDV for the treatment of COVID-19 [99]. On the other hand, the NIH advises to include RDV for hospitalized patients receiving noninvasive O_2 supplementation or those at high risk for disease progression. An already initiated RDV course should be completed in patients progressing to WHO stages 5 and beyond [100]. Starting RDV in mechanically ventilated patients is not recommended.
b. **Molnupiravir (EIDD-2801)** is currently undergoing phase II/III trials. Earlier work has shown effective inhibition of viral replication of SARS-CoV-2 *in vitro* and in animal models [101]. In two dose-escalation studies in outpatients with mild COVID-19, molnupiravir was safe, well-tolerated, and shortened viral shedding compared to placebo [102, 103]. While molnupiravir did not benefit hospitalized patients, a phase II/III study is currently investigating its impact on hospitalization rate, clinical characteristics and mortality in outpatients with mild to moderate COVID-19. Its oral bioavailability may be an asset in the ambulant setting [104].
c. **Favipiravir** has been evaluated in mild to moderate COVID-19 patients, most not requiring oxygen[105], was well-tolerated, and accelerated viral clearance. It is now undergoing further study in outpatients[106].

Novel antiviral agents continue to be developed[107], such as PF-07304814, a SARS-CoV-2 protease inhibitor for which phase 1 results are awaited (NCT04535167). Several agents are in pre-clinical development, and more data is likely to become available over the following months.

2. Blocking (co)-receptors, preventing viral entry into host cells.
a. Recombinant human ACE2 (**rhACE2) receptor** [108] as decoy therapy has been used, to some encouraging effect, in a small case series of patients with non-COVID-19 associated ARDS [109], suggesting a mechanism of action other than viral neutralization. Instead, rhACE2 may restore homeostasis of the ACE2/Ang1-7/MasR system, as lack of ACE2 mediates both epi- and endothelial inflammation (see below). Concerns for negatively impacting pulmonary autoregulation have not been substantiated [482].

b. In addition to ACE2 binding, viral entry requires proteolysis of the spike protein by the host-enzyme TMPRSS2 [110], which is androgen-dependent, which may account for some of the observed risk

disparity. Serine protease (TMPRSS2)-inhibitors such as **nafamostat** and **camostat mesylate** [111, 112] are being explored for use in mild COVID-19 [113]. The latter expedited recovery by 40% in outpatients with mild disease by day five [114] but had no impact on clinical improvement, admission rate to intensive care or mortality in hospitalized patients [115]. Since nafamostat also inhibits fibrinogen proteolysis, it has been proposed as a short-acting anticoagulant at later disease stages [116-118]. Single reports of cerebral bleeds on this treatment require careful consideration [483].

c. **Maraviroc,** an inhibitor of chemokine receptor CCR5, is used widely in HIV therapy. Maraviroc inhibits the viral SARS-CoV-2 protease *in vitro* [119]; and is currently being evaluated in phase II trials in ventilated COVID-19 patients (300mg BD for 14days, NCT04441385, NCT04435522) as well as in patients with moderate disease (NCT04710199). Animal data suggest that this compound may also have additional benefits by reducing neutrophil recruitment to the lung in severe COVID-19 [120].

None of these treatments is recommended outside clinical trials yet.

3. Anti-SARS-CoV2 monoclonal antibody preparations

While recommended in the beginning of the pandemic, bamlanivimab and tesevimab, the recent emergence of escape variants has led to their replacement by new antibody preparations.

a. REGN-CoV2 contains two anti-spike receptor-binding-domain (RBD)-antibodies, **casirivimab** and **imdevimab**. In SARS-CoV-2 positive outpatients, one dose accelerated viral clearance and symptom resolution (13 vs 6 days) among seronegatives [121]. The effect on seroconverted individuals was less pronounced. An RCT assessing 2.4g or 8g of casirivimab/imdevimab, administered within 7 days from symptom onset in SARS-CoV-2-positive outpatients reduced medically attended visits in the combined treatment group compared to placebo by half (6% vs. 3% overall), and from 15% to 6% in seronegative patients [122]. Data indicates that REGN-CoV2 benefits outpatients with mild COVID-19, who are at risk for disease progression

b. Results for **VIR-7831** (Sotrovimab), a monoclonal antibody with Xtend technology prolonging its half-life and expected to enhance pulmonary absorption, has been assessed in SARS-CoV-2 infected outpatients with mild or moderate illness (COMET-ICE trial). A single i.v. dose of 500mg resulted in a subsequent reduction of relative risk for hospitalization or death by 85% compared to placebo (p=0.002) [123].

c. **Nanobodies** are antibody fragments consisting of a single monomeric variable antibody domain occurring naturally in camelids and sharks. Nanobodies with a high affinity for spike protein, effectively competing with ACE-2 and recognizing epitopes that are structurally not accessible to conventional antibodies are being explored as neutralizing antiviral agents, currently at the pre-clinical stage [124, 125].

4. Hydroxychloroquine (HCQ)

Among its many anti-inflammatory and anti-thrombotic effects, HCQ interferes with viral uptake and intracellular transport by altering the endosomal pH. However, HCQ failed to demonstrate an impact on clinical outcome or survival in exposed presymptomatic individuals [126, 127], including those with mild disease [128, 129], those hospitalized with or without O_2 requirement and with severe COVID-19 [130, 131]. HCQ prolongs the QT interval, which, particularly in patients with underlying cardiac problems, is another argument against its widespread use [132]. Two metanalyses on the effect of HQC in combination with Azithromycin demonstrated an increase in mortality among hospitalized patients (RR 1.27 [1.04-1.54]; RR 1.11 [1.02,1.20]) [134, 133].

5. Ivermectin (IVM)

This anthelminthic agent has received attention as an inhibitor of intracellular viral transport *in vitro*, however at MICs well above what would be safely achievable *in vivo* [135]. Heterogeneity of data available has complicated their interpretation [137]. A recent metanalysis of 10 RCTs in 1173 patients

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evaluating its use in COVID-19 has not identified a clinical or survival benefit [136]. The use of IVM is not recommended outside of clinical trials.

Take home messages for this stage:
1. Timing of antiviral therapies is likely critical but due to lack of data no recommendations for their use in outpatients can be made
2. Post exposure prophylaxis with selected anti-SARS-CoV2 monoclonal antibody preparations are recommended in high risk individuals
3. Agents blocking (co)-receptors, preventing viral entry into host cells remain under investigation with some having shown clinical benefit
4. Hydroxychloroquine has failed to demonstrate any clinical or survival benefit for all disease stages
5. The use of ivermectin is not recommended outside of clinical trials

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3. **WHO 9 point Scale, Patient Stage 2. Infection, Ambulatory, limitation of activities**

At this disease stage, patients may display signs of a lower respiratory tract infection or mild pneumonitis with cough and fever.

Alveolar macrophages (AMs) are the first line of defense and respond to PAMP/TLR signaling triggered by infected alveolar epithelial cells (AEC)[138]. Both produce pro-inflammatory cytokines (IL1β, IL8, IL18, TNFα , IFNγ) and chemokines (CXCL2) that recruit peripheral immune cells to the lung. Epithelial infection also downregulates regulatory ligands, removing the tolerizing epithelial interaction with, and disinhibiting, AMs [139, 140].

The viral receptor ACE2 is part of the ACE2/angiotensin-(1-7)/MAS axis of the Renin-Angiotensin-System[141], which counteracts the pro-inflammatory and vasoconstrictive effects of Angiotensin 2 (AT2) by cleaving it to Ang1-7 [142]. After binding SARS-CoV-2, ACE2 is internalized [143-145], and AT2 will accumulate as a result. Mediated by the Angiotensin 2 receptor 1 (AT1R)[146-148], AT2 upregulates endothelial adhesion molecules, facilitates leukocyte recruitment [141, 149], and polarizes macrophages towards a pro-inflammatory M1 phenotype [150-153]. The conversion of AT2 by ACE2 into anti-inflammatory Ang1-7 is impaired, and excess AT2 damages epi- and endothelial integrity through its inflammatory, vasoconstrictive and pro-fibrotic effects [154]. ACE2 downregulation induced by SARS-CoV-2 infection exacerbates a pro-inflammatory state, causing lung damage that may exceed the initial viral cytopathic effect [144, 145].

The key questions at this disease stage are:
   a. **how likely the patient will progress to more severe disease based on his/her risk profile and**
   b. **which biomarkers should be measured to assess the risk for progression**

Most risk scores have been validated in hospitalized patients, and little is available to help with stratifying risk in outpatients [155-157].
An acuity score predicting hospitalization, intensive care admission, or mortality risk in COID-19 patients based on 30 parameters performed well. Blood pressure, respiratory rate and SaO2 were the most relevant predictors, feasible in most outpatient settings [158].

Biomarkers indicative of innate immune cell activation and epithelial damage are now useful to predict disease progression. CCR5, IL1ra and IL10 may predict a severe disease course up to a week prior to clinical deterioration [159]. Until such specific biomarkers become widely available, it is important to consider vital signs and laboratory parameters that are accessible without delay. These include hsTroponin, proBNP, IL-1, LDH, transaminases, renal function, inflammatory markers and coagulation

testing which indicate early extrapulmonary end organ involvement and have been shown to assist with clinical assessment and guide management decisions (discussed below).

Based on published evidence about this disease stage, therapeutic recommendations include:

1. Antiviral therapy
As discussed above, antivirals may theoretically be of benefit but have not been sufficiently studied in outpatients. The development of RDV preparations for inhalation in outpatients considered at risk of progression may add therapeutic options before admission becomes necessary [93, 160].

2. Anti-SARS-CoV2 monoclonal antibody preparations
The recommendations for the use of anti-SARS-CoV2 monoclonal antibody preparations as discussed above apply for this disease stage as well.

3. Interferon III (IFN- λ)
IFN- λ is exclusively expressed by respiratory and gastrointestinal epithelia. Hematopoietic cells lack IFN- λ receptors, and therefore it has little systemic pro-inflammatory effect. With a favorable safety profile observed in phase II hepatitis D trials [161,162], IFN- λ seems an attractive candidate for COVID-19 therapy. Initial data on IFN- λ use in outpatients (180mcg once s/c) showed accelerated viral clearance if IFN- λ was administered within five days of symptom onset compared to placebo [163]. Others, administering IFN- λ within three days of symptom onset, did not find such benefit [164]. The side effect profile was favorable, with transient transaminitis being the main reported adverse event.

4. Budesonide
GCs may downregulate ACE2 in respiratory epithelia [165] and reduces airway inflammation, possibly impacting the beginning of epithelial and macrophage-driven host response. The STOIC trial of and age-stratified cohort with mild COVID-19 symptoms for less than seven days. Intervention was open-label, 800mcg Budesonide dry powder inhalation BD until symptom resolution compared to SOC. Medically attended visits and hospitalizations were fewer (14% vs 1%; p=0.004), and symptom resolution faster (7 vs 8 days, p=0.007) [166]. The treatment was well-tolerated, encouraging larger placebo-controlled trials that target mildly affected outpatients

- ### *Convalescent plasma (CP)*
CP has been widely administered to patients with COVID-19, often with advanced disease. Patients may have already seroconverted and have neutralizing anti-SARS-CoV2 concentrations equivalent to those contained in CP [167] **(Table 1)**. CP may contain pro-inflammatory and pro-coagulant factors [168]. Further, SARS-CoV2 specific antibody titers vary greatly [169]. Antibody kinetics in COVID-19 differ: nonsurvivors have a delayed antibody response, whereas survivors produce neutralizing antibodies more rapidly [170]. Based on this observation and considering the abovementioned caveats, the *timing* of exogenous antibody administration seems critical.
As the majority of studies on CP use have been uncontrolled, it is not surprising that efficacy assessments of a metanalysis including 30 studies and RCTs with 17.225 patients [171] were inconclusive ("very uncertain") and found no effect on mortality or clinical improvement at 28 days.
CP outside of clinical trials is no longer recommended, except for patients with impaired humoral immunity. A recently published open-label RCT on CP use in 921 hospitalized patients was terminated early for futility. The risk for intubation or death by day 30 did not differ (32.4% in the CP group, 28.0% in the SOC group; RR 1.16; [0.94–1.43] $P = 0.18$) and patients receiving CP experienced more serious adverse events (33.4% versus 26.4%; RR = 1.27, 95% CI 1.02–1.57, $P = 0.03$)[172].

- ### *AT1R blockers, ACE-inhibitors (ACEi)*
This drug class was initially hypothesized to impact COVID-19 outcomes either by restoring homeostasis of the ACE2/Ang1-7/Mas-R system; or conversely by upregulating tissue-resident ACE2. A metanalysis

of 21 studies[173] did not support a difference in risk of death (pooled OR 1.29 [0.89-1.87] p=0.18) or disease severity (pooled OR 0.94 [0.59-1.50] p=0.81) in patients who had been receiving ACEi when contracting SARS-CoV-2. Since then, several studies assessing the impact of discontinuing ACEi treatment upon COVID-19 diagnosis have not identified a difference in disease severity or death. Discontinuation of ACEi/ARB treatment in those already using these agents is therefore not justified.

- *Azithromycin (AZM)*

Besides its antimicrobial properties, AZM has immunomodulatory effects. It repolarizes macrophages towards tissue-restorative M2 and inhibits pro-inflammatory NFκB and STAT1 signaling [174, 175]. However, in patients with a moderate oxygen requirement (WHO stage 4), AZM did not impact progression to MV or death [176]. As macrolides prolong the QTc interval, their use should be carefully monitored, especially in older patients or in combination with other pro-arrhythmogenic agents. Most studies have investigated AZM in combination with HCQ and repeatedly identified an increased mortality risk associated with this combination [133]. AZM is therefore not recommended in the treatment of COVID-19.

> **Take home messages for this stage:**
> 1. Risk assessment in mildly symptomatic outpatients should integrate demographic factors, extent of respiratory symptoms, neutrophil/lymphocyte ration, inflammatory markers and biomarkers of extrapulmonary tissue injury
> 2. Anti-SARS-CoV-2 monoclonal antibody preparations are recommended in high risk individuals
> 3. Inhaled budesonide in ambulatory patients not requiring oxygen may be beneficial but requires more detailed assessment
> 4. Evidence does not support the use of azithromycin and, especially in combination with HCQ, may inflict harm.

4. WHO 9 point Scale, Patient Stage 3 Hospitalized, no O2 requirement

Hospitalization becomes necessary in approximately 4.7% of infected individuals. The risk in patients over 60 years is higher – approximately between 10 and 20% [30]. The decision to admit patients not requiring O_2 will be informed by a comprehensive assessment of clinical, laboratory and imaging findings [177], with more pro-active management of risk groups and the availability of healthcare resources.

Several clinical scores have been developed to distinguish those at risk for disease progression at the time of hospitalization (**Table 2**). A moderately accurate prediction of future severe COVID-19 disease can be achieved by combining the results of CT findings of the lung, inflammatory markers (C-reactive protein, ferritin, neutrophils, lymphocytes, albumin), evidence of tissue injury (transaminases, LDH, Troponin, D-Dimer) and evidence of electrolyte imbalance (blood urea, electrolytes)[178]. Lymphopenia and neutrophilia, expressed as elevated NLR (neutrophil/lymphocyte ratio) on admission are consistently associated with disease progression and death [179, 180].
A metanalysis of 5699 patients showed that an elevated NLR on admission increased the risk of death almost threefold (RR2.74 [0.98-7.66][181]. Leukocytosis, elevated LDH, procalcitonin, and transaminitis were associated with increased risk of ICU admission and death [32], while lymphopenia, elevated CRP and fibrinogen on admission predicted an O_2 requirement [182]. Another metanalysis including 4969 patients found that neutrophilia and lymphopenia on admission was associated with a significantly increased risk of progression to severe COVID-19 (OR 7.99; 1.77-36.14 resp. OR 4.2; 3.46-5.09,) and death (OR 7.87; 1.75-35.4, resp. OR 3.71; 1.63-8.44) [183].

Biomarkers that may be helpful to assess risk for disease progression at this stage reflect activation of innate immunity, immune cell recruitment, and beginning damage to epithelial and endothelial barriers and tissue injury.

Blood samples of COVID-19 patients show significantly higher levels of circulating endothelial cells (CECs) on admission than those with other respiratory infections, demonstrating **early and extensive endothelial injury** [184]. Epithelial and endothelial damage begins long before a patient is admitted to the ICU, and CECs, if available, may be of prognostic value now [185]. Other markers of endothelial activation with discriminatory value at this stage are von Willebrand Factor (vWF), angiopoietin (Angpt-1/Angpt-2 ratio, see below) and soluble urokinase plasminogen activator receptor (suPAR). Early discharge and mild disease trajectory have been predicted by a suPAR of ≤2ng/mL with high specificity [186].

Of all cytokines measured in over 1400 COVID-19 patients at hospitalization [187], IL-6 and TNFα levels independently predicted disease severity and death, outperforming CRP, D-Dimers and ferritin. Higher CRP, IL-6, IL-8, IL-10, TNFα and IL-2R levels on admission were found in those patients later progressing to critical illness and/or death [188].
Hospitalization and progression to severe disease could also be predicted by a decision algorithm integrating demographic risk factors and comorbidities with immune cell profiling [189].
At this stage, replicating virus may rarely be present in blood [190, 191]. Viremia and RNAemia in COVID-19 increase the risk of critical disease and death six to elevenfold [192-194].

Considering more widely available markers, the combination of elevated LDH, CRP and decreased lymphocyte counts predicted ten-day mortality [195]. The combined analysis of the patient's age, CD4$^+$ lymphocyte counts and LDH was a clinically useful composite for disease progression (AUC 0.92) [196]. In summary, markers of inflammation (CRP, ferritin), cardiac (troponin, BNP), epithelial (Angpt-2) and endothelial injury (CECs), combined with pre-existing clinical risk factors, may provide the best assessment for disease progression. Angpt-2 and CECs may also be helpful biomarkers in patients at risk for disease progression before an O_2 requirement develops but may not be widely available.

The Lung Injury Prediction Score (LIPS) assessed the risk of ARDS at time of hospitalization in a variety of conditions [197-201]. Even though not validated for COVID-19 ARDS, its positive predictive value for this indication was enhanced significantly when Angiopoietin 2 (Angpt-2), CRP, and the FiO2/SpO2 ratio within 6h of admission were included.

Multiorgan involvement, including coagulopathy, myocardial, liver, intestinal and kidney injury, may all precede respiratory manifestations[202, 203]. Myocardial injury on admission in particular predicts poor outcome, especially if both troponin and proBNP are elevated. Higher troponin levels on admission are accompanied by higher D-Dimers, fibrinogen, creatinine, WBC, and procalcitonin levels, reflecting organ involvement beyond the respiratory and cardiac systems.
In a metanalysis published by Figliozzi et al., evidence of acute cardiac injury was by far most predictive for poor outcome (OR 10 [5-22.4]), followed by renal injury and low platelet and lymphocyte count [204]. Metadata from 10 clinical studies generated two predictive equations including CRP, neutrophil, lymphocyte count +/- D dimer, resulting in a sensitivity of 0.76 (0.68) and specificity of 0.79 (0.83) when applied to a cohort of patients [205].

Future works must emphasize parameters that predict deterioration at a time point when therapeutic interventions can counteract disease progression. Based on a recent UK study on COVID-19 patients presenting to the emergency department, strict implementation of simple clinical observations while considering demographic risk factors outperforms the prognostic value of laboratory biomarkers [206].

Finally, a recent study reports that Anti-DNA and anti-phosphatidylserine antibodies, determined at hospital admission, correlated strongly with progression to severe disease (PPV 85.7% and 92.8%). Antiphospholipid antibodies have been observed in COVID-19 patients since the very beginning of the pandemic [207]. This suggests that autoantibodies following the initial viral insult contribute to the pathology at later stages of COVID-19.

Based on published evidence about this disease stage, therapeutic recommendations include:

1. Antiviral therapy.
The WHO no longer recommends antivirals for hospitalized patients. NIH guidelines however suggest that RDV may be used in hospitalized patients at high risk of disease progression with or without oxygen requirement (WHO stage 3, 4).

2. Corticosteroids:
RECOVERY assessed dexamethasone in hospitalized patients of varying severity. There was no benefit seen in patients who did not require ventilatory support (OR 1.19; 0.91-1.55) [208] or in those with early disease (symptom duration <7days) [208]. Concerns for early steroid use would include immunosuppression at a time when viral replication may still be very active [209, 210]. In a metanalysis of five RCTs including 7692 patients, steroid use in patients without O_2 requirement was even associated with an increased mortality risk (RR 1.23 [1.00-1.62]; p=0.05) [211]. In summary, there is presently no evidence to support the use of steroids at WHO stage 3.

2. Interferons
Interferons (IFN), produced by lymphocytes (Type II: IFN-γ) and epithelia (Type III: IFN-λ) are some of the most effective antiviral defense mechanisms. Type I IFNs (IFNα, IFNβ) initiate an antiviral response through their receptors INFAR1/2, widely expressed on epithelial, endothelial and myeloid cells. INFAR engagement activates Janus Kinase (JAK1), which mediates inflammation and antiviral effects [212]. While the use of a pro-inflammatory signaling molecules seems counterintuitive initially, *the timing of IFN-I* administration in relation to viral replication is critical. The replication of SARS-CoV-2 is reported to peak already at symptom onset. A rapid IFN-1 response controls viral replication, whereas a delayed IFN-1 rise results in excessive inflammation and tissue damage instead [82, 213-215].
In critically ill COVID-19 patients, IFN-1α and β responses are impaired, virus persistence is prolonged and systemic inflammatory markers are comparatively high [216, 217]. SARS-CoV-2 produces only a weak early IFN-1 response *in vitro* [217]. A suppressed early IFN-1 response may allow viral replication to peak unopposed and contributes to the excessive inflammation seen in patients with severe disease [213, 214]. It follows that exogenous IFN-1 should be beneficial early, while delayed administration could easily be harmful [218].
Results of important IFN trials are summarized in **Table 3.** The Solidarity trial assessed IFN-β1a therapy at WHO stages 3-6. It failed to demonstrate a survival benefit overall and suggested worse outcomes among ventilated patients.
Three trials in hospitalized patients (WHO stages 3-5) treated with either IFN-β1b s.c. for two weeks or nebulized IFN-β1a resp. IFN-α2b within five days of admission suggested accelerated clinical improvement, reduced ICU admissions and lower mortality [219]. Treatment more than five days after admission however *increased* mortality (aHR 0.05 [0.01-0.37] early treatment, 6.8 [1.41-40.8] p=0.2 late treatment) [220].
In a phase II placebo-controlled study of nebulized IFN-β1a [221] in hospitalized patients, at WHO stages 3 and 4, IFN treatment still reduced the risk of severe disease or death significantly even though median symptom duration was ten days (OR 0·21 [0·04–0·97]; p=0·046). IFN-I may therefore retain a benefit for longer than suggested, at least in the noncritically ill [222].

3. Heparin

The International Society for Thrombosis and Hemostasis (ISTH) recommends low molecular weight heparin prophylaxis for all hospitalized patients with COVID-19 and supports its continuation for 2-6 weeks following discharge [223, 224].

The benefit of heparinization leading to improved organ support free survival in noncritically ill *hospitalized* patients has now been backed up by results from ATTACC/ACTIV-4a/REMAP-CAP and CORIST studies (see below). In the noncritically ill hospitalized group, therapeutic anticoagulation may be superior to prophylactic dosing, but more data is required [225, 226].

- ***Anti-SARS-CoV2 monoclonal antibody preparations***

Monoclonal antibodies failed to demonstrate a benefit in hospitalized patients [227, 228], and are no longer recommended regardless of oxygen requirement, except in patients with humoral immunodeficiency [229].

Take home messages for this disease stage:
1. Patient risk stratification for disease progression is a critical step during this diseases stage. Clinical risk scoring systems could assist this, in conjunction with immune cell profiling, imaging results and appropriate biomarkers
2. Interferon therapy, administered within 3-5 days of admission may be of benefit at this stage but more evidence is needed for a recommendation to be made.
3. Heparin prophylaxis should be initiated in all hospitalized patients with COVID-19
4. The use of GCs and monoclonal antibodies at this stage is not recommended

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5. WHO 9 point Scale, Patient Stage 4 Hospitalized, O_2 requirement by mask or nasal prongs

The reported rate of patients progressing to stage 4 varies widely, but a large proportion of those admitted will require oxygen supplementation. Mortality in this group can be significant, even in those not dyspneic at presentation[230].

In a subset of patients, the controlled antiviral response transitions to a dysregulated immune response during this WHO stage, possibly even earlier. The clinical presentation is now characterized by ongoing respiratory epithelial and endothelial damage, followed by excessive recruitment of activated innate and adaptive immune cells. The most relevant immunopathologic processes, which in our opinion characterize stage 4 and overlap in many aspects with stages 3 and 5, are outlined below.

a. *Disrupted AT2/ACE2 homeostasis*

The downregulation of ACE2 in cells infected by SARS-CoV2 leads to elevated AT2 levels, vasomotor disturbance, increased ventilation-perfusion (V/Q) mismatch (ventilation of non-perfused lung areas), microcapillary leaks, and epithelial apoptosis [143-145]. AT2's pro-inflammatory effects via NFkB [141] enhance leukocyte-endothelial interactions through upregulation of ICAM-1 and VCAM-1, setting the stage for NETosis and thrombotic complication (see below) [231, 232].

b. *Macrophage activation and polarization*

Monocytes and macrophages are key elements of the early antiviral response, dominate the developing dysregulated inflammatory process, and are the drivers for cytokine excess, neutrophil and lymphocyte recruitment, development of barrier dysfunction and tissue fibrosis [233, 234].

Depending on their environment, macrophages exist on a spectrum from pro-inflammatory M1, responsible for pathogen killing, production of reactive oxygen species (ROS) and proinflammatory cytokines (IL1b, TNFα, IL6, IL18) [235], to M2 cells with a focus on phagocytic activity, promoting immune tolerance, fibrosis and tissue repair [236-238]. Non-inflammatory removal of apoptotic

immune cells, *efferocytosis*, is a unique feature of M2 macrophages [239]. Activated alveolar macrophages (AM) [138, 140] recruit bone-marrow derived monocytes to the lung [240, 241], where they adopt an M1 phenotype, complementing the antiviral response but also amplifying tissue damage [242] and initiate massive neutrophil recruitment and activation of Th1 and Th17 cells [243]. Histopathology of autopsied lungs of patients with COVID-19 ARDS implies a crucial role for macrophage activation and the subsequent neutrophil migration [244, 245]. The persistence and prolonged activation of M1 macrophages result in an excess of pro-inflammatory mediators, reactive oxygen species, enzymes and accumulating cellular debris all of which is detrimental to epi/and endothelial integrity [235, 246-248]. Once the inflammatory stimulus is removed, M1 must revert to M2 macrophages to begin a "clean up and repair program" and deactivate the previous "pro-inflammatory program". Otherwise, the inflammatory process will persist [249, 250]. One of the factors inhibiting the repolarization to M2 is netosis, thereby exacerbating tissue damage [251].

c. Activation of the VEGF-Angpt-1/2-Tie2 system

High Angpt-2 levels predict ICU admission at the time of hospitalization [252]. Patients with Angpt-2 levels above 5000pg/mL were 10 times more likely to require ICU care (OR 9.33 [2.35-44.9]). Angpt-2 was the only blood parameter correlating with compliance measures during MV (mL/cmH$_2$O, $r = -0.46$, $p = 0.01$) and renal function, emphasizing the prognostic relevance of biomarkers of endothelial activation and microvascular damage during this stage.

Pulmonary neutrophil recruitment may be associated with further significant clinical deterioration and escalation of respiratory support [244]. Therefore, a high NLR as well as markers of epithelial and endothelial damage (low VEGF2R levels and low Angpt-1/2 ratio (see below) is expected to have prognostic value at this stage [202, 253-256].

Based on published evidence about this disease stage, therapeutic recommendations include:

1. Antiviral therapy: see recommendations as detailed under prior WHO stages

2. Steroids: GCs have many anti-inflammatory properties, including the repolarization of macrophages towards M2 and inhibition of neutrophil recruitment [257, 258].
The RECOVERY trial yielded landmark data on the role of GCs in COVID-19, and its results emphasize the importance of timing of therapeutic interventions. It studied hospitalized patients at WHO stages 3, 4 and 5ff treated with **dexamethasone** (6mg OD i.v./p.o.), for 10 days (n= 2104) to SOC (n=4321) and demonstrated a 28 day survival benefit in mechanically ventilated (29.3% vs 41.4%; HR 0.64 [0.51-0.81]) or O$_2$ dependent patients at WHO stage 4/5 (23.3.% vs 26.3%; HR 0.82[0.71-0.94]); but no benefit in those without O$_2$ requirement (17.8% vs 14.0%; HR 1.19 [0.91-1.55]) [208]. GCs were only beneficial if the symptom duration was *longer* than 7days.
A metanalysis of seven studies (n=1703) [259] addressed GCs in COVID-19 patients with an at least moderate O$_2$ requirement; most were ventilated. GCs decreased the 28 day mortality (HR 0.66 [0.52-0.83], p<0.001), in those mechanically ventilated or on noninvasive ventilation (noninvasive O$_2$: HR 0.41 [0.19-0.88]; MV: HR 0.69 [0.55-0.86]), whereas *patients requiring inotropes did not benefit* (HR 0.55 [0.34-0.88] vs 1.05 [0.65-1.69]; p=0.06). Another metanalysis of 7692 patients similarly identified a benefit of steroids, limited to patients requiring MV (RR 0.85 [0.72; 1.00, p=0.05][211]. In summary, data is consistent showing that steroids are beneficial at later disease stages, in patients requiring oxygen or MV (see below).

3. IL-6 inhibition
Increased IL-6 expression by monocytic cells in COVID-19 [260] provides a rationale for the use of IL-6 blockers (Sarilumab, Siltuximab, Tocilizumab (TCZ)). An IL-6 level of >30pg/mL at hospitalization indicated a future need for MV in a cohort of 146 patients [261].

Table 4 summarizes relevant studies on IL-6 inhibition in hospitalized patients specific to WHO stages at recruitment. The results indicate in most that risk of progression to MV is decreased when IL-6 inhibition is initiated at WHO stage 4 or 5.

Recovery has been the largest trial investigating IL-6 inhibition [265]. It recruited hospitalized patients mainly at WHO stages 4, 5 and 6, most (82%) received concomitant GCs. In patients at stage WHO 4 and 5, 28-day mortality (HR 0.81 [0.67-0.99]; HR 0.96 [0.74-1.00]), respectively and the risk of progression to MV was reduced (15% vs 19%; HR 0.79; 0.69-0.92; p=0.002). At WHO stage 6, a survival benefit was not as evident (HR 0.93 [0.74-1.18])[265] and overall was only present when GCs were given concomitantly (RR 0.79 [0.7-0.89] vs 1.16 [0.91-1.48].

A recent metanalysis of 27 trials including 10.930 patients at WHO stages 3, 4, 5, IL-6 blockade (TCZ n=18, sarilumab n=9) compared to placebo or SOC confirmed these findings. 28-day mortality (22% vs 25%; OR 0.86 [0.79-0.95]) and risk of progression to MV were both reduced in the IL-6 inhibitor group. Again, the benefit was limited to a combination with GCs (OR 0.78 [0.69-0.88]). IL-6 blockade alone did not achieve a mortality reduction (OR 1.09 [0.91-1.30])[266]. Another more recent metanalysis of 28 cohort studies and 8 RCTs showed again that the risk for progression to MV was reduced (RR 0.84 [0.76-0.93]) in WHO stages 4 and 5 and a survival benefit limited to those receiving concomitant GCs [267].

In summary, Tocilizumab is recommended *in combination with steroids* for recently hospitalized patients at WHO stage 4-5, with rapid disease progression or who require MV for less than 24 hours [268].

A double-blinded RCT including 457 and 1365 patients randomized and treated in phases 2 and 3, respectively, assessed the use of sarilumab. Among the 20% of phase 3 patients receiving MV, a third of whom also received steroids, the proportion with ≥1-point improvement in clinical status at day 22 was 43.2% for sarilumab and 35.5% for placebo (RRR 21.7%). In analyses combining phase 2 and 3 patients requiring MV, the mortality risk was reduced, though non-significantly (HR 0.76; [0.51 to 1.13]). Again patients receiving GCs concomitantly showed more pronounce risk reduction (OR 0.49 [0.25 to 0.94]).

4. IL-1-inhibitors:

IL-1-inhibitors in the form of the endogenous receptor antagonist IL-1ra (anakinra) or as monoclonal antibody against IL-1β (canakinumab) showed promise in cohort and observational studies [269-274] that triggered further investigations. Evidence remains controversial, but the timing of administration yet again seems crucial.

A randomized trial [275] compared the addition of anakinra to SOC in patients at WHO stage 4ff. No difference was seen between the groups in mortality by 28 days (22% vs 24%, aHR 0.77 [0.33-1.77]), oxygen wean, or time to discharge.

When patients requiring oxygen were randomized to receiving anakinra within ≤4days from admission, early treatment reduced 28-day mortality by 74% (aHR 0.26 [0.1-0.66], p<0.001) compared to SOC. No survival benefit was seen in patients not in the early treatment group who may have received anakinra as late rescue therapy (aHR 0.82, p=0.7). These results allow some attribution of benefit to use at earlier disease stages [276] and illustrate how critical the clinical status at the time of treatment allocation is. A recent metanalysis of IL-1 inhibition in COVID-19 could not proceed due to the data heterogeneity between studies [277]. A suPAR level of >6ng/mL heralds the development of respiratory failure in COVID-19 [278] and may assist biomarker-guided IL-1 inhibition [279].

Two recent studies failed to demonstrate a benefit of IL-1 inhibition with canakinumab compared to SOC. Patients were included at WHO stages 4 and 5, and neither MV free survival nor risk of COVID-19 related death differed significantly [280]. Additional reasons for the lack of canakinumab benefit in COVID-19 are likely based on the pharmacokinetic profile of this drug and its selective inhibition of IL-1β, leaving IL-1α unopposed [281].

At present, pending further data collection, IL-1 inhibition is not recommended as SOC in COVID-19 management.

5. Janus-kinase-inhibitors (JAK inhibitors)

Many immune reactions responsible for the inflammatory response in COVID-19 (including IFN-1a,b) are transcriptionally regulated by the JAK-STAT pathway[282, 283]. A metanalysis [284] of five studies investigating JAK inhibition in COVID-19 demonstrated a significant reduction in mortality (HR 0.12 [0.03-0.39]), and ICU admission (OR 0.05 [0.01-0.26]). **Table 5.**

In two early studies in hospitalized patients, most of whom with an O_2 requirement but not requiring MV, treatment with *Baricitinib,* an oral JAK1/JAK2 inhibitor, for seven days on LPV/r +/- HCQ background, demonstrated a faster reduction in O_2 requirement and a lower mortality rate (1/20 (5%) vs 25/56 (45%) compared to SOC [285]. A follow-up study mainly included patients at WHO stages 3/4 [286]. Here, the need for intensive level care at 14 days was significantly reduced in the treatment group, and patients were more likely to be discharged by two weeks (77.8% vs 12.8%, p<0.0001).

TACTIC-R [289] is assessing the combination of baricitinib with *ravulizumab* (a C5 inhibitor) in WHO stages 3-5. Although treatment with *ruxolitinib*, an oral JAK1/2 inhibitor, was shown to be safe, it did not reduce mortality or progression to MV in patients at WHO stages 4 and 5 [290].

In a recent study assessing *tofacitinib* in the treatment of hospitalized patients at WHO stages 3, 4 and 5 (including high flow O2 only) [291], the cumulative incidence of death or respiratory failure through day 28 was reduced by 37% (RR 0.63; [0.41 to 0.97] p=0.04). All-cause mortality was observed in 2.8% of tofacitinib and 5.5% of placebo-treated patients, but the effect was not significant (HR 0.49; 95% CI, 0.15 to 1.63). Serious adverse events were not significantly more common in the treatment group (14.1% vs 12.0%). Potential safety concerns for JAKi include a rise in creatinine kinase, transaminases, and myelosuppression, which may increase the risk of opportunistic infections. The complete blood count should be monitored during treatment.

6. TNF α inhibitors (TNFi)

Data on the use of TNFi in COVID-19 is limited. In a small study including seven patients, three of which were already mechanically ventilated, Infliximab at a dose of 5mg/kg iv on days one and three [292], resulted in a rapid decrease of pro-inflammatory cytokines and a clinical improvement in six of seven patients. In comparison, the mortality rate in the 17 control patients at a similar stage of hospitalization was 35%. The ACTIV trial (NCT04593940) recruits hospitalized patients with moderate to severe COVID-19 (WHO stage 4ff) and will, in addition to infliximab, assess abatacept and cenicriviroc, an inhibitor of chemokine receptors CCR2 and CCR5, for this indication.

7. GM-CSF inhibition – or supplementation?

GM-CSF, among other functions as overall pro-inflammatory cytokine and growth factor, polarizes macrophages towards M1 and upregulates integrin expression by neutrophils, mediating their adhesion to and migration across endothelium. Higher serum levels of GM-CSF in ARDS correlate with a higher risk of death [293]. Antagonizing GM-CSF, therefore, appears to be an attractive target in COVID-19 [213]. The best time for GM-CSF inhibition, based on immunopathology, would be *prior* to the recruitment of peripheral monocytes. GM-CSF inhibition has an established safety record [294], but neutropenia, alveolar proteinosis, and impaired viral clearance remain concerns. In addition, lack of GM-CSF inhibits phagocytosis, efferocytosis by M2 macrophages and impairs the removal of NETs which may delay macrophage repolarization.
Conversely, GM-CSF is critical for AM survival, surfactant removal, epithelial protection and the antiviral response. Higher GM-CSF levels in ARDS bronchoalveolar lavage fluid are associated with better outcomes [295-297], contrasting the association of higher serum levels with a worse prognosis [298, 299]. Despite initial concerns for excessive granulocyte mobilization and recruitment of neutrophils to the lung [295], first data assessing inhaled GM-CSF (sargramostim 125mcg, BD, for 5 days) in hypoxemic patients are encouraging [300].

Addition of sargramostim for five days to SOC in patients at WHO stages 4 and 5 was associated with a P(A-a)O$_2$ improvement by $\geq$ 33% compared to SOC alone (54% vs 26%, p<0.001, NCT04326920). In a second cohort, including patients at WHO stage 4 and those requiring high flow oxygen but not NIV, oxygenation was also improved (treatment group 84%, SOC group 64% p=0.02)[301].

Amplifying pulmonary neutrophil recruitment might worsen the patient's respiratory status. Under this premise, GM-CSF receptor blockade is also under investigation in COVID-19. **Mavrilimumab** (i.v. 6mg/kg once) showed some promise in a small prospective cohort study from Italy in patients at WHO stages 4 and 5 [302].
A double-blinded RCT recruited 40 patients in WHO stages 4 and 5 (n=21 receiving mavrilimumab) and found no significant difference in mortality or oxygen wean to placebo. However, mortality was high overall (43% and 53%, respectively) [303]. An ongoing study comparing mavrilimumab to placebo in hospitalized patients at WHO stages 4 and 5 reported in an interim analysis of n=166 that MV-free survival was higher in the treatment arm (86.7% vs 74.4%, p=0.1), equivalent to a 65% risk reduction, with final results outstanding [485].

8. Interventions targeting NETosis. Netosis is probably one of the most important yet underrecognized mechanisms in the pathophysiology of COVID -19. The release of Neutrophil Extracellular Traps, or NETosis, is a defense system utilized by neutrophils against bacteria, viruses or protozoa. During the formation of neutrophil extracellular traps (NETs), the neutrophil nuclear membrane is dissolved and NETs consisting of chromatin, citrullinated histones (CitH3), neutrophil elastase (NE) and oxidative enzymes such as myeloperoxidase are released into the extracellular space [304-306]. Excessive NETosis damages epithelial [307] and endothelial [308] cells. NET removal by two extracellular enzymes, DNase I and DNaseIL3, expressed by dendritic cells and macrophages, is critical for tissue homeostasis [309]. NETs promote M1 persistence in COVID-19 and delay macrophage repolarization, which prevents the degradation of cellular debris by M2, facilitated by C1q [251]. As a result, efferocytosis, a hallmark feature of M2 cells, cannot occur effectively. Proinflammatory cytokines continue to be released, which prevents a timely switch to tissue-restorative repair processes [247, 248, 310]. NETs are also highly prothrombotic. They entrap erythrocytes and platelets and can form intravascular NET clots [309, 311]. Autopsies of COVID-19 victims show this featuring thrombotic occlusion of pulmonary, cardiac, renal, and hepatic vasculature by aggregated NETs [312, 313].
NETosis can be quantified by measuring specific biomarkers (cell-free DNA, myeloperoxidase [MPO]-DNA, and citrullinated histone H3 [Cit-H3])[314]. These correlate closely with SOFA scores [315, 316] and may be useful for risk stratification at earlier disease stages.
Dornase alfa is commonly used in inhaled form for patients with cystic fibrosis where it cleaves extracellular DNA, mainly from leukocytes, thereby decreasing the viscosity of respiratory secretions [317]. Beneficial effects on recovery in small case series in critically ill COVID-19 patients with ARDS have been published, additional trials are underway [318], [319], [320, 321]. Other DNAse enzymes for the treatment of hospitalized patients with acute moderate to severe SARS-CoV-2 infection are currently in development.

9. Heparin
The ATTACC trial compared therapeutic-dose heparinization as an initial strategy in *non*critically ill patients, most at WHO stage 4 with SOC thromboprophylaxis. There was a trend favoring therapeutic-dose heparinization (survival to discharge: 76.4% vs 80.2%), exclusive to this earlier disease stage[225], but more data is required.

10. 2-deoxy-2-Glucose:
2-DG was granted EUA by the Indian authorities for moderate and severe COVID-19 when faced by the overwhelming pandemic impact on the Indian subcontinent[322].

It inhibits glycolytic ATP production and is used to sensitize tumor tissue to chemo- and radiotherapeutic agents. 2-DG administration followed by low dose radiation was suggested as a means to reduce lung inflammation in COVID-19 [323]. The agent accumulates in metabolically active, virus-infected cells and results in their apoptosis. Phase 3 trials recruited patients at WHO stage 4ff, without adding radiation. Early oxygen wean was more frequently possible (42% vs 31%), but more evidence to support this treatment is needed, and detailed data on safety is lacking.

> **Take home messages for this disease stage:**
> 1. Data strongly support the use of GCs at this stage. Careful monitoring for secondary infections in these patients is critical.
> 2. JAK-inhibitors offer a benefit in terms of preventing progression to MV and survival
> 3. IL-6 inhibition, in combination with GCs, is recommended at this and later disease stages
> 4. While results from larger trials with IL-1 inhibitors are lacking, data available from observational cohorts suggests that they may have a benefit on clinical outcome and survival in this but not later disease stages.
> 5. The administration of GM-CSF antibodies can currently not be recommended while the use of inhaled GM-CSF may be of benefit at this and later stages
> 6. Enzymatic therapy with DNAse 1 or recombinant DNAse-L3 to counteract Netosis may play an important role in preventing progression of COVID-19 in this disease stage. However, data of clinical trials are still pending.

6. WHO 9 point Scale, Patient Stage 5: Noninvasive ventilation or high flow oxygen

Driven by inflammatory cell recruitment and barrier dysfunction, patients at this stage have progressed to severe pneumonia, and their gas exchange is more severely affected. They require high flow oxygen, and approximately one fifth will require noninvasive pressure support [324].

The three main immunologic mechanisms during this stage include:

1. Disruption of endothelial and epithelial integrity

Worsening capillary leakage and alveolar edema now contribute to poor gas exchange [325, 326].
The main determinants of endothelial and epithelial permeability are the VEGF and Ang/Tie2 systems.
The primary stimulant of VEGF production by AECs is IL-1β [327-329]. Under normal physiologic conditions, pulmonary VEGF levels of capillary and alveolar lumens are strictly compartmentalized [330]. During an infection with SARS-CoV-2 this compartmentalization is lost, resulting in worsening epithelial damage [331] and release of alveolar-side VEGF into the bloodstream across the damaged barrier [332]. This promotes endothelial Angpt-2 release [331], amplifying capillary leakage [333]. Therefore, an increase of VEGF in the alveolus (as detectable in bronchoalveolar lavage fluid) indicates improved barrier function and predicts recovery from ARDS [334] while increasing plasma levels are associated with worsening pulmonary edema [335, 336].
Angpt-1 is the main agonist of the endothelial Tie2 receptor [337, 338]. Their interaction seals endothelial tight junctions and protects against capillary leakage [339-345]. It opposes Angpt-2 action on Tie2 [342, 346], which increases capillary permeability [342, 347, 348] and leads to epithelial apoptosis [325, 346, 349-353].
Increased Angpt-2 and low VEGF2R levels in plasma predict ARDS severity and 28d mortality [336]. In mechanically ventilated patients, serum Angpt-2 correlates with the severity of pulmonary vascular leakage and predicts the likelihood of ICU admission, development of ARDS and resulting fatality in COVID-19 [252, 354-360]. A low Angpt-1/Angpt-2 ratio is a marker for endothelial dysfunction and a consistent feature of adverse outcomes in sepsis, DIC and ARDS [361-369].

2. Neutrophil Recruitment and Amplification of Inflammation

Much of COVID-19-associated inflammatory pulmonary damage is mediated by M1 macrophages and the neutrophils they recruit [55, 370-372]. Neutrophilia, especially in the BAL fluid, is a consistent feature of severe COVID-19 and predicts mortality [28, 190, 202, 253, 255, 373-375]. Autopsies of COVID-19 patients have demonstrated the accumulation of neutrophils and M1 macrophages associated with microangiopathic and thrombotic changes in pulmonary capillaries [376-378]. Especially in patients who require respiratory support, the neutrophil population contains immature, lower density granulocytes (LDGs) [256]. LDGs are ineffective phagocytes [256, 312, 379-382], produce large amounts of pro-inflammatory cytokines (IL17, IFN-I) and have a propensity to form NETs [383, 384].

CXCL5 concentration in BAL fluid correlates with the extent of neutrophil infiltration of lung parenchyma [385, 386].

The damaged alveolar epithelium, in turn, activates the endothelium, which upregulates adhesion molecules [387-389], and mechanically entraps primed neutrophils [390 392]. This close interaction with the activated endothelium activates the neutrophils, which causes them to release inflammatory mediators, form NETs [312, 390] and enter the alveolus [371].

In summary, neutrophils home to the COVID-19 lung, interact with the damaged endothelium and contribute to tissue damage. Because of NETosis-induced impairment of macrophage repolarization, efferocytosis is defective. Accumulating NETs may not be adequately removed and sustain inflammation and neutrophil recruitment, further exacerbating inflammatory tissue injury.

3. Immune thrombosis

Thromboembolism complicates up to a third of COVID-19 admissions to ICU [393-397]. Generalized endothelial damage and thrombotic microvascular injury of lungs, kidneys, liver and heart and frequent pulmonary embolism [396] and stroke [398], characterize severe disease.

Evidence for endothelial dysfunction is present as early as WHO stage 3. Levels of FVIII, vWF:Ag, D-Dimers at the time of hospitalization correlate with risk of thromboembolic complications and mortality in COVID-19 patients [182, 399, 400].

Not all markers of endothelial damage have equal prognostic value, and more data are required in this area. Thrombomodulin, selectin, Angpt-2 and CEC levels were all significantly elevated in patients with more severe COVID-19, but in a comparative analysis, only vWF antigen discriminated disease severity of outpatients, non-critical (WHO stage 3,4,5) and critical (WHO stages 5,6,7) COVID-19 [401, 402]. Other selected markers of endothelial damage may predict inpatient mortality (glycocalyx damage (AUC 0.74), ADAMSTS13 (AUC 0.73) and VEGFA (AUC 0.73)), but will not be readily accessible to most clinicians [403].

4. Complement activation

The complement system has antiviral properties [404] but can also result in tissue injury through activation of Netosis and pro-coagulant effects. The pivotal role of complement activation in COVID-19 was identified early [405]. Histopathology of skin, kidney and lung biopsies from COVID-19 patients (n=5) showed extensive deposition of C5b-9 in the microvasculature [406]. Complement pathways are highly induced in the COVID-19 lung, which correlate with disease severity [407-409].

Based on published evidence about this disease stage, therapeutic recommendations include:

1. Antiviral therapy: remains indicated as discussed above

2. Steroids*:* remains indicated as discussed above

3. Heparin: remains indicated as discussed above

4. Cytokine inhibitors: As discussed above, IL-6 inhibition can be expected to be of benefit. The data for IL-1 inhibition is less clear but on balance would favor earlier use (WHO stage 4)

5. JAK inhibitors: Based on the ACTT-2 and COV-barrier results, JAK inhibition has most impact at this stage.

ACTT-2, a double-blinded, placebo-controlled RCT enrolled over 1,000 inpatients at WHO stage 4ff to assess efficacy and safety of **baricitinib** 4mg OD for 14 days in addition to RDV versus RDV alone. Patients receiving GCs were excluded. Baricitinib addition made progression to MV or death less likely (HR 0.69; [0.5-0.95]). Patients on high flow O_2 or NIV (WHO stage 5) benefitted most. Here, time to clinical recovery was shortened from 18 to 10 days and clinical improvement by two weeks was twice as likely (OR 2.2 [1.4-3.6]). In patients at WHO stage 3, 4 or 6 however, baricitinib did not impact time to recovery. Secondary infections were less frequent in the treatment arm [287].

The COV-barrier trial [484], a recently published double-blinded, placebo-controlled phase 3 RCT assessed baricitinib in addition to SOC among hospitalized COVID-19 patients, over 90% of who also received GCs. Overall 28-day mortality in the treatment group was significantly reduced (8% vs 13%, HR 0·57 [95% CI 0·41–0·78], p=0.002), and clinical improvement at day 4 through 14 was more likely. Patient at WHO stage 5 (NIV or high flow O2) again benefited most (28-day mortality HR 0·52 (95% CI 0·33–0·80); p=0·006). The baricitinib benefit was maintained in those who did not receive concomitant GCs or RDV, and persisted when mortality risk was re-analyzed at 60 days (HR 0.62 [0.47-0.83] p=0.005).

In summary, baricitinib appears to have its most significant benefit at WHO stage 5. It is currently recommended in combination with remdesivir only which, given recent evidence, may be revised [288].

6. Angiopoietin 2 inhibitors, VEGF inhibitors

Vanucizumab, a bispecific monoclonal antibody directed against Angpt-2 and VEGF, usually used as an angiogenesis inhibitor in solid tumors [410], is currently undergoing trials in COVID-19.

Similarly, inhibition of VEGF as the main factor stimulating Angpt-2 release may be of value, especially as it enters the circulation in severe lung injury. *Bevacizumab,* a monoclonal VEGF-A antibody, has now been repurposed for use in COVID 19 (NCT04275414; NCT04305106) in patients meeting ARDS criteria.

In a study of 26 patients, treatment with i.v. bevacizumab resulted in improved PaO2/FiO2 within 24h and rapid normalization of inflammatory markers [411]. However, the clinical status of the cohort was very diverse, complicating the interpretation of these findings. A case series in COVID-19 patients requiring ICU level care [412] included n=25 receiving bevacizumab, and n=21 receiving a combination of TCZ/ bevacizumab. 23/25 (93%) of bevacizumab treated individuals recovered to discharge, as did 14/21 patients receiving a combination treatment. Dosing and WHO stages of the patients were not reported, and more research is required before an assessment of its benefit can be made.

*7. Tie-2 mimetics***:** *Vasculotide,* a Tie2 mimetic improved survival in animal models of viral pneumonia and ARDS and reduced pulmonary edema and endothelial apoptosis [413-415]. Clinical trials investigating AV-001/Vasculotide and similar products in human ARDS and COVID-19 are planned .

8. Complement inhibition: Monoclonal antibodies targeting specific complement factors, **eculizumab and ravulizumab** inhibiting C5, or AMY-101 inhibiting C3, are currently undergoing assessment in COVID-19 studies. So far, available data is limited to uncontrolled smaller case series.

At WHO stage 5ff (>6L/min O2 requirement, severe pneumonia, or ARDS), eculizumab 900 mg on D1, 8, 15, and 22 in addition to SOC was associated with lower 28-day mortality (7/35 (20%) vs 23/45 (51%), p=0.005), and respiratory support could be weaned faster [416]. A trial assessing ravulizumab in 122 patients with severe COVID-19 (WHO stage 6ff) was halted after interim analysis did not support efficacy [419]. Assessment of patients not yet requiring MV (WHO stage 5) is being evaluated. Selective C5a inhibition in severe COVID-19 has been investigated by Vlaar and colleagues[420]. C5a is a strong chemoattractant of neutrophils, leads to endothelial activation and is central to neutrophil tissue-factor dependent pro-coagulant activity [421, 422]. Administration of seven i.v. doses of C5a inhibitor *vilobelimab* in 15 patients with severe COVID-19, mainly at WHO stages 5 and 6 did not impact early

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oxygen wean or mortality compared to SOC (aHR 0·65 [95% CI 0·10–4·14]). Thromboembolic complications though were less frequent (2/15 vs 6/15). Given these initial results, vilobelimab is undergoing further assessment in severe COVID-19 (NCT04333420). In summary, despite some studies showing rapid decline of inflammatory markers, sufficient evidence supporting the use of complement inhibitors outside of clinical trials is lacking [416-418]

9. Statins: Statins inhibit MyD88, upstream of NFκB, and have several anti-inflammatory and immunomodulatory effects. Earlier metadata suggests a risk reduction of 30% for progression to severe COVID-19 or death with the use of statins [423]. A more recent metanalysis including seven retrospective cohort studies (2398 patients) found that COVID-19 patients taking statins had nearly 40% lower odds of progressing to the composite endpoint of severe/critical illness or death (OR: 0.59; [0.35–0.99]). This was even more pronounced in patients taking statins pre-admission (OR 0.51 [0.41-0.64]). The addition of simvastatin to SOC in patients with ARDS due to a variety of pathologies showed that only those with a hyperinflammatory phenotype, defined by IL-6 and sTNFr1 levels, benefited from statins. In this subgroup, the improvement achieved in 28 day mortality and ventilator- resp, organ support- free survival was significant [424]. While this does not address whether or not adding statins acutely would be of benefit, these findings may be relevant to future research on COVID-19 related ARDS.

10. Imatinib is a Bcr-Abl tyrosine kinase inhibitor and approved chemotherapeutic agent for Philadelphia chromosome positive CML and ALL. Experimental and early clinical evidence suggests that imatinib protects the integrity of the vascular barrier [425, 426]. It has been studied in severe COVID-19 with the rational of mitigating damage to the barrier of the alveolo-capillary unit. In a double-blinded placebo-controlled RCT [427], 400 patients at WHO stages 4ff were assigned to either placebo or imatinib at a loading dose of 800mg followed by 400mg OD for nine days. Three-quarters of participants received concomitant GCs, a fifth RDV; no other immunomodulatory agents were used. Time to discontinuation of MV or oxygen wean did not differ, while time spent on MV was shorter (survivors 7 vs 12 days, p=0.02) and 28-day survival improved (mortality risk aHR 0·52 [0·26–1·05]; p=0·068).

Take home messages for this disease stage:
1. Risk stratification based on clinical findings and biomarkers is critical
2. Currently available data strongly support the use of GCs in patients at this disease stage.
3. Heparin: remains indicated as discussed above
4. JAK inhibitors remain indicated as discussed above
5. Although data remain limited, monoclonal antibody directed against Angpt-2 and VEGF may play an a role in preventing the progression to MV in this disease stage
6. IL-6 inhibitors are recommended under certain conditions at this stage
7. Data is not sufficient to recommend the use of complement inhibitors or imatinib at this disease stage, but new data on a potential role for these agents is emerging

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7.   WHO 9 point Scale, Patient Stage 6 – Intubation and Mechanical Ventilation

At this stage, patients progress from requiring high flow oxygen to intubation and MV. The clinical deterioration at this stage is a direct consequence of the inflammatory and immunologic mechanisms initiated at stages 3 and 4 that are now leading to respiratory failure.
In over 10,000 hospitalized COVID-19 patients from Germany, mortality was 53% among those who progressed to MV, compared to 16% who did not [324, 428].
Autopsy results in mechanically ventilated patients who had rapidly progressed to severe respiratory failure demonstrated neutrophilic invasion of the alveolar spaces and microvasculature, epithelial injury and microthrombi, likely related to excessive neutrophil recruitment to the lung [244].

Based on published evidence about this disease stage, therapeutic recommendations include:

1. Steroids are beneficial in COVID-19 patients requiring MV (see under WHO stage 4).

2. Antibiotic and Antifungal treatment:

Prolonged immunosuppression in the critically ill must be navigated with caution. Secondary bacterial and fungal superinfections frequently complicate severe COVID-19, and patients must be closely monitored. Increasingly, COVID-19 associated invasive mycoses are being recognized, due to profound lymphopenia, prolonged significant illness, and immunosuppressive therapies [429].

3. Heparin

There is a high incidence of isolated pulmonary artery thrombi in critically ill COVID-19 patients suggesting the possibility that some thrombotic events in these patients are formed in situ rather than representing dislodged emboli [430]. While thromboembolism is very common in COVID-19, heparinization does not completely abolish this risk [431-433], and thromboembolic events despite prophylactic, and even therapeutic heparinization occur.

Biomarkers of NETosis such as cell-free DNA are significantly elevated in patients at WHO stage 5. Many factors contribute to the prothrombotic state in severe COVID-19, with NET formation and antiphospholipid antibodies emerging as important contributors [312]. Lastly, heparin resistance is not uncommon in severe COVID-19 [434], and alternative strategies for anticoagulation may have to be pursued, such as direct thrombin inhibition with argatroban [435]

There was early recognition that anticoagulation should be administered in COVID-19 patients, but heparin dosing has been controversial [436, 437](**Table 6**). The International Society on Thrombosis and Haemostasis (ISTH) suggests risk stratification with dose escalation to intermediate (50% increase of prophylactic dose) for those with a BMI ≥30 or very high D-Dimers (≥3000) and *discourages the use of therapeutic doses for primary prevention [223]*. The ATTACC/ACTIV-4a/REMAP-CAP trial[438], where therapeutic anticoagulation was *inferior to usual care thromboprophylaxis* in the outcome of organ-support free survival, with a higher incidence of major bleeding complications, lends support to this approach. This sets critically ill COVID-19 patients apart from those with moderate illness (WHO stages 3,4,5) in whom therapeutic heparinization was not inferior (see above).

4. Aspirin (ASA)

ASA has a favorable anti-inflammatory effect on the neutrophil-platelet-endothelial interaction which results in microthrombi, VQ mismatch and NETosis.

The data on treatment with ASA in non-COVID-19 ARDS in at-risk individuals is controversial [439, 440]. One study even showed an association with an increased risk of MI, VTE and stroke [440].

5. IL-6 Inhibitors

In addition to the use of IL-6 inhibitors as discussed under WHO stage 4, siltuximab (in one to two doses) was used in a small cohort study including 30 patients on either NIV support or MV matched to patients receiving SOC [441]. The majority received concomitant GCs (18/30). The 30-day mortality rate was significantly lower in the treatment group (HR 0·46, 95% CI 0·22– 0·97); p=0·04). Though not all patients had completed the follow-up period, 16/30 were discharged, four remained on mechanical ventilation, and ten patients died. This contrasts the findings of the much larger Recovery trial on TCZ, and evidence on siltuximab will have to be revisited as more information becomes available.

6. IL-1 Inhibitors

In a cohort study comparing TCZ, Sarilumab and anakinra in patients at stages 5 and 6, IL-1 and IL-6 inhibition improved long-term (180 days) survival when initiated before the establishment of severe ARDS (PaO2/FiO2 < 100 mmHg). Notably, in this cohort that did not co-medicate patients with GCs, all three agents offered a survival benefit in patients requiring MV (180-day mortality risk. Anakinra HR 0.47 [0.26-0.87], sarilumab HR 0.55 [0.25-1.22], TCZ HR 0.57 [0.28-1.14]). In patients with severe

ARDS, the survival advantage offered by sarilumab and tocilizumab was lost (TCZ HR 1.02 [0.37-2.81], sarilumab HR 0.69 [0.25-1.75]), and while the efficacy of anakinra was reduced, it was still superior to SOC (HR 0.46 [0.22-0.94])[442].

Take home messages for this disease stage:

1. The use of GCs in patients with COVID-19 has been found to be most beneficial for patients in this disease stage. Careful monitoring for secondary infections in these patients is critical
2. Starting antiviral therapy in this disease stage is no longer recommended
3. Heparin at prophylactic dose remains indicated. A proposed risk stratification guiding heparin dosing is discussed above. The additional use of ASA and NSAIDs cannot be recommended
4. The use of IL-6 inhibitors may be beneficial
5. Drugs targeting Netosis might be critical in this disease stage but data from clinical trials are still pending.
6. Despite limited data the use of complement inhibitors for this stage cannot be recommended

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8. WHO 9 point Scale, Patient Stage 7 – Ventilation and additional organ support

Stages 6 and 7 are pathophysiologically similar and characterized by gradual deterioration of widespread endothelial damage [443]. Approximately 33% of hospitalized patients may progress to COVID-19 associated ARDS [444].

Acute respiratory distress syndrome (ARDS) is the result of dysregulated inflammation in response to a pulmonary or systemic insult that impacts the endothelial and epithelial integrity of the alveolocapillary unit [445]. Clinical data suggest ARDS endotypes with distinct clinical features and disparate outcomes [445, 446]. The clinical course of ARDS is described as occurring in two stages [361, 447]:

a. an inflammatory exudative phase characterized by alveolar-epithelial damage, recruitment of inflammatory cells with subsequent alveolar flooding with proteinaceous fluid, formation of hyaline membranes, and resultant hypoxemic respiratory failure (week 1-2)

b. a fibroproliferative phase characterized by lung fibrosis and vascular remodeling (week 2-3ff)

The Berlin ARDS criteria define an international diagnostic standard [447, 448].

COVID-19 associated ARDS, as evidenced by autopsy studies, is consistently characterized by

- extensively affected microcirculation, alveoli infiltrated with neutrophils and/or monocytes/macrophages
- peripheral neutrophilia and decrease of most lymphocyte subsets (i.e., a high NLR), correlating with poor outcome, higher sequential organ failure assessment (SOFA) scores and death [28, 190, 202, 253, 255, 373, 374].
- a highly inflammatory pulmonary response, often in combination with ongoing viral RNA presence
- extensive diffuse alveolar damage
- widespread endothelial damage and thromboembolic events

The pandemic has put a spotlight on the fact that despite therapeutic advances, the overall mortality of ARDS remains unacceptably high[36]. Therefore, the most critical strategy in COVID-19 management is addressing the evolving inflammation-mediated tissue damage early. Ventilatory strategies, fluid balance and positioning are the most important points and foundations of ARDS management once it occurs but are well beyond the scope of this review. Pharmacologically, in addition to steroid administration, the therapeutic focus shifts to addressing the epithelial and endothelial barrier dysfunction – especially if the Angpt2/1 ratio or circulating VEGFR2 levels remain elevated. The patient's prognosis may be reflected in

NLR, coagulation parameters, D-Dimers, von Willebrand factors, Troponin, BNP, renal and liver function, CECs (circulating endothelial cells), and NETosis markers such as cell free DNA (see above).

Based on published evidence about this disease stage, therapeutic recommendations include:
Treatment recommendations in this disease stage are essentially identical to those for WHO stage 6.
1. ***Steroids*** are of benefit in COVID-19 patients who are mechanically ventilated
2. ***Antibiotic and Antifungal treatment***: Prolonged immunosuppression in the critically ill will have to be navigated with caution. Secondary bacterial and fungal superinfections frequently complicate severe COVID-19. Patients must be closely monitored for secondary infections. Increasingly, COVID-19 associated aspergillosis (CAPA) is being recognized, resulting from profound lymphopenia, and as a complication of immunosuppressive therapies [449].
2. ***Statins****:* as discussed at WHO stage 5
3. ***Mesenchymal stem cells (MSC):***
The use of MSC in severe ARDS is experimental and only included here for completeness and to introduce this novel treatment concept. It is a common misperception that MSCs in ARDS replace damaged alveolar cells. In fact, the proposed clinical benefit is ascribed to their immunomodulatory properties, skewing macrophages to M2, and exerting an antifibrotic effect. Available data is minimal. The COVID-19 Treatment Guidelines Panel of the NIH recommends against the use of mesenchymal stem cells for the treatment of COVID-19 outside of clinical trials.

> **Take home messages for this disease stage:**
> 1. Ventilatory strategies, fluid balance and positioning are the most important points and foundations of ARDS management
> 2. The use of GCs are of benefit at this disease stage.
> 3. Due to prolonged immunosuppression and the critical condition of patients in this disease stage, active surveillance for secondary infections and antibiotic and antifungal treatment play an important role
> 4. Heparin remains indicated at prophylactic dose, with some data indicating that therapeutic dosing may inflict harm
> 5. The initiation of antiviral therapy in this disease stage is no longer recommended
> 6. The use of MSC in this disease stage is experimental and evidence insufficient to recommend it

9. Summary

Therapeutic options for patients with COVID-19 are rapidly evolving, and knowledge gained from currently ongoing clinical trials may change future treatment recommendations. We believe that sound treatment decisions are based on a thorough understanding of the immunopathology of COVID-19. This understanding will enable clinicians to develop a well-defined treatment strategy based on clinical risk scores, immune cell profiling, disease-stage specific biomarkers, laboratory and imaging findings. We recognize that during disease progression, pathological processes overlap, influence each other, and new ones may emerge. Especially at earlier disease stages, treatment target the prevention of a dysregulated hyperinflammatory state. We believe this occurs at the latest at WHO stage 4 in predisposed individuals. Once patients require mechanical ventilation, treatment becomes increasingly challenging with fewer effective treatment options and a higher risk of adverse outcomes. Consequently, a disease-stage specific treatment selection should not be made empirically but follow published evidence from the literature as summarized above.

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Table 1. Relevant trials assessing convalescent Plasma (CP) in COVID-19 (selection)				
Study	Design, n	WHO stage of included patients, administered dose	outcomes	
Li [450]	RCT, n=103	4-13 mL/kg, variable titers Severe COVID (23/22), life threatening COVID (29/29)	Time to improvement at28d by 2OSP: overall Severe COVID Life threatening COVID-19 28D mortality	HR 1.4 (0.79-2.49) HR 2.15 (1.07-4.32) HR 0.88 (0.3-2.63) HR 0.59 (0.22-1.59) No effect on time to improvement or mortality, possible signal for clinical benefit in severe but not life threatening COVID-19
Agarwal[451]	PLACID, RCT open label n=464	moderate COVID-19 (SaO2≤93% in RA, PaO2/FiO2 200-300)	Progression to severe COVID (PaO2/FiO2 ≤100) 28D mortality	HR 1.04 (0.54-1.98) HR 1.04 (0.66-1.63) No effect on mortality or disease progression
Gharbharan [167]	ConCOVID, n=86, RCT	Hospitalized, not MV≥4d, but otherwise not well defined	Mortality Clinical improvement D15	79% of patients had antibodies at baseline HR 0.95 (0.2-4.7) HR 1.3 (0.52-3.32)
Abolghasemi [452]	open label RCT, N=189	Mod. COVID-19 (stages 4,5), hospitalized for ≤3d, O2 requirement, not intubated	28D mortality Progression to MV	14.8% vs 24.3% , p=0.09 7% vs 20.3%, p=0.006
Simonovich [453]	PlasmAR, RCT, n=333	Hospitalized, with O2 requirement (any). Almost all received steroids	30D mortality Improvement on ordinal scale D14	HR 0.83 (0.52-1.46) HR 1.00 (0.65-1.55) No significant benefit in severe COVID
Joyner [454]	Observational, n=35.322	Hospitalized, ICU: 52.3% MV: 27.5%	7D mortality pts who received high-titer CP, no MV 7D mortality in pts treated with CP within 3d, no MV 7D mortality in those treated < vs ≥3d after diagnosis 30D mortality in those	14% vs 11%, p=0.03 6.3% vs 11.3%, p=0.0008 8.7% (8.3-9.2%) vs 11.9% (11.4-12.2%), p≤0.001 21.6% vs 26.7% , p≤0.001

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			treated < vs ≥3d after diagnosis	
Joyner [455]	retrospective, n=3082	WHO stage 4,5,6,7	30D mortality (high titer CP) 30D mortality (high titer CP), not MV 30D mortality (high titer CP) MV (low titer and/or already on MV – no benefit. Data not shown)	HR 0.75 (0.61-0.93) HR 0.64 (0.46-0.88) HR 0.93 (0.73-1.19)
Chai [456]	Cochrane review, 19 observational studies and RCTs	N=38.160 patients (36.081 received CP) RCTs: n=189 (95 received CP)	Mortality Improvement of clinical symptoms at D7 Improvement of clinical symptoms at D15 Improvement of clinical symptoms at D30	HR 0.64 (0.33-1.25) RR 0.98 (0.3-3.19) RR 1.34 9 0.85-2.11) RR 1.13 (0.88-1.43)
Recovery	RCT, open label, n=10406	Not released, pre-publication communication to investigators	28D mortality	HR 1.04 (0.95-1.14)

Table. 2 Clinical Risk Score in hospitalized patients with COVID-19			
	Symptom/marker on	**OR disease progression to ICU**	**OR death**

		admission	or critical illness	
Liang [177]	Chest x-ray abnormal	3.39		
	Hemoptysis	4.53		
	Dyspnea	1.88		
AUC 0.88	Level of consciousness	4.71		
	History of malignancy	4.07		
	NLR raised	1.06		
	LDH raised	1.02		
	Bilirubin raised	1.15		
	Number of comorbidities	1.60		
Ciceri [457]	>65 years of age		3.17	
	History of coronary disease		2.93	
	Lymphocytes <0.9x10^9		1.83	
	Higher RALE score		1.05	
	LDH above median		2.95	
	D-Dimer above median		2.54	
Stefanini [458]	hsTroponin		1.32	
	Lymphocytes		0.52	
AUC 0.88	Age		1.1	
	O_2 requirement		2.55	
	Tachypnoea >20/min		1.84	
	Tachycardia >100/min		0.36	
	Fever		2.12	
	GFR <60mL/min x1.73m		2.19	
	Malignancy		2.38	
	D-Dimer		1.51	
	Age		1.13	
AUC 0.92	GFR<60mL/minx1.73m^2		2.66	
	hsTroponin AND BNP		3.24	
	D-Dimer		1.00	
	Lymphocyte		0.19	
	SaO_2 desaturation		2.07	
Masetti [459]	Age >75years		10.6	
	Thrombocytopenia <150x10^9/L		3.64	

	Ferritin >750ng/mL		3.33
Henry [183], (metanalysis)	Lymphopenia	4.2	3.7
	Neutrophilia	7.99	7.87
	Lymphopenia <0.5 x10^9/L		12.0
Hao [179]	SpO$_2$	5.67	
	Fever	2.36	
Hospitalization	Age	2.4	
	Tachycardia	2	
	Diastolic BP	4.51	
	Dyspnoea	7.41	
	Chronic kidney disease	2.25	
ICU	Chest x-ray opacity	4.08	
	Tachypnoea	1.66	
	Age	1.76	
	Fever	1.83	
	Male	1.63	
	Hypoalbuminemia	1.78	
	SpO2	2.29	
	LDH	2.62	
	Ca^{2+}	1.73	
Mechanical ventilaion	CRP	1.53	
	LDH	6.47	
	Ca^{2+}	1.79	
Feng [460]	Age	1.06	
	NLR	1.74	
	CT severity score	1.19	
Jain [461]	Progression to severe disease	Dyspnea 3.7	
	Progression to ITU	Dyspnea 6.5	
Li [188]	hsTrop, CK, LDH	See text	
Caricchio [178]	Six criteria predicting cytokine storm, see text	Predicted cytokine storm/ use of cytokine blockade	

Table 3.: Studies assessing interferon for use in COVID-19 (selection)			
Study	DESIGN, N	WHO STAGE OF INCLUDED	OUTCOMES

		PATIENTS, ADMINISTERED DOSE		
Solidarity [462]	RCT, open label, n=2050	INFβ1a 3x 0.44mcg s/c or iv for 1week. WHO stages 3-6 In air n=482/490 O₂ req. n=1429/1430 Ventilated n=139/130	28 day mortality MV No MV	HR 1.16 (0.96-1.39) HR 1.4 (0.82-2.4) HR 1.1 (0.84-1.45)
Rhamani [219]	RCT, open label, n=80 (33/33)	INFβ1b 250 mcg s/c for 2 weeks, combined with LPV/r/ ATV/r and HCQ. WHO stage 4 (6% IFN group), 5 (75% IFN group), 6ff (18% IFN group)	Time to clinical improvement Discharge D14 ICU admission 28D mortality	9(6-10) vs 11 (9-15), HR 2.30, p=0.002 78.8% vs 54.6%, OR 3.09, p=0.03 14 (66.7%) vs22 (42.4%), p=0.04 2 (6%) vs 6 (18.2%), p=0.12
Davoudi-Monfared [463]	RCT, n=92 (46/46)	IFNβ1a 0.44mcg s/c, 3x weekly for 2 weeks. combined with LPV/r, HCQ, GCs. SaO₂≤90%, median symptom duration 10d	D28 discharge D28 overall mortality Progression to MV Mortality early IFN (<10d) Mortality late IFN (>10d)	31 (73.8%) vs 23(58.9%), OR 1.96(0.8-5) 8 (19%) vs 15 (43.6%), p=0.015 35% vs 44%, p=0.33 OR, 13.5;95%CI 1.5-118) OR, 2.1; 95%CI 0.48-9.6
Estebanez [464]	Observational retrospective. N=256 (106/150)	IFNβ1b at 250mcg s/c for 1-2 weeks on alternate days, combined LPV/r, HCQ or TCZ, GCs. (mild 26%, moderate 36%, severe 18%) median symptom duration 7d	Mortality	20.8% vs 27.3% p=0.229
Hung [465]	RCT open label, n= 127 (86/41)	IFNβ1b s/c 8mio IU for 1-3 doses. Combined with LPV/r, ribavirin. Most WHO stage 3	Time to SARS-CoV-2 PCR neg Clinical improvement Length of hospitalization	7d vs 12d (RR 4.37 (1.86-10.24) p=0.001 4d (3-8) vs 8d (7-9), p<0.0001 9d vs 14.5d
Wang [220]	Retrospective, observational	IFNα2b, Early= within 5d (48%) Late= after 5d (5.8%) No IFN (45.7%). Most WHO stage 3,4,5	In-hospital mortality Early IFN vs no IFN Late IFN vs no IFN Age >60y	Early (0.9%), late (15.4%), non (4.9%) aHR mortality 0.05 (0.01-0.37), p=0.004 aHR mortality 6.82 (1.14-40.8), p=0.005 HR mortality 6.87 (p≤0.001) – treatment independent.
Pereda [466]	Observational N=814	IFNα2b 3x per week for 2 weeks, i.m.	Note: 75% of control group but 5.5% of treatment group on ICU	

		Majority combined with LPV/r, HCQ	at inclusion Discharge Fatality rate overall Fatality rate for severe disease	145 (95.4%) vs 6(26.1%) 7 (0.9%) vs 17 (32.1%) 7 (21.9%) vs 17 (48.5%)
Monk [222]	Blinded, placebo controlled RCT, n=101 (50/51)	Nebulized IFNβ1a 6mio IU once daily for 14d, WHO stage 3, 4,5, median symptom duration 10d (7-11d)	Recovery D15 Recovery D28 Discharge D15 Discharge D28 Improvement D15 Improvement D28 Progression to ICU/severe disease	OR 3.19 (1.24-8.24) OR 3.58 (1.41-9.04) OR 1.63 (0.61-4.35) OR 1.84 (0.64-5.29) OR 2.32 (1.07-5.04) OR 3.15 (1.39-7.14) OR 0.21 (0.04-0.97) p=0.046

Table 4. Interleukin-6 inhibition in COVID-19 (selection)				
Study	DESIGN, N	WHO STAGE INCLUDED, DRUG ADMINISTERED	OUTCOMES	RESULT
COVACTA [468]	Multinational RCT, N=452	8mg/kg Tocilizumab iv once or twice. Hospitalized patients at WHO stage ≥4. Co-administration of SOC except: immunomodulators other than GCs	Median ordinal scale D28 Median ordinal scale D14 Mortality overall D28 Median ordinal scale D28 if MV Need for ICU transfer	1.0 (TCZ); 2.0 (1.0-4.0) placebo, p=0.31 3.0 (2.0-4.0) TCZ; 4.0 (3.0-5.0) placebo 19.7% TCZ; 19.4% placebo; p=0.94 5.0 (3.0-5.0) TCZ; 5.0 (4.0-6.0) placebo 21.3% TCZ; 35.9% placebo
EMPACTA [469]	Double-blinded, placebo-controlled RCT, n=249	8mg/kg Tocilizumab i.v. Hospitalized patients at WHO stage ≥4. Excluded if requiring pressure support, >50% received steroids	Progression to MV or death, (composite) overall Mortality Overall	12.0 (8.5-16.9)% TCZ; 19.3 (13.3.-27.4)% placebo; HR 0.56; p=0.04 11.6% TCZ; 11.8% placebo; p=N.S.
BACC BAY[470]	Double-blinded, placebo-controlled RCT, n=243	8mg/kg Tocilizumab single dose. majority WHO stage 3 (supplemental oxygen only). GCs in 6% placebo, 11% TCZ	Mortality D28 Time to ICU admission or death Oxygen weaned at D14	10.6 (6.7-16.6) TCZ; 12.5 (6.9-22)% placebo, p=0.64 15.9 TCZ; 15.8% placebo, p=0.97 75.4% TCZ; 78.8% placebo, p=N.S.
CORIMUNO-TOCI[471]	RCT, n=131	Tocilizumab 8mg/kg, repeat if no improvement	28D mortality	7/64 (89%) TCZ, 8/67 (88%) SOC; HR 0.92 (0.33-2.53)

		GCs in 33% Patients at WHO stage ≥3	Oxygen weaned by D28	89% TCZ; 75% SOC; HR 1.41 (0.98-2.01)

Table 5. Jak-inhibitor trials in COVID-19 (selection)				
Study	DESIGN, N	WHO STAGE INCLUDED, DRUG ADMINISTERED	OUTCOMES	RESULT
Bronte [472]	Observational, n=96 (n=20 treatment/ n=76 control)	Baricitinib 4mg BD for 2d, then 4mg OD for 1 week. Clinical stage not specified.	narrative	Faster reduction in O2 supplementation
Cantini [286]	Observational, retrospective. N=192 (78/113)	Baricitinib. Moderate COVID-19. FiO_2 200-300. No GCs given	14D mortality ICU admission at 2 weeks Discharge at 2 weeks	0% vs 6.4% , p=0.01 0.88% vs 17.9%, p≤0.001 77.8% vs 12.8%, p≤0.0001
Cantini [285]	observational, n=24 (12/12)	Baricitinib 2 weeks, combined LPV/r, HCQ. mild-moderate COVID-19, SaO_2 <93%	Mortality ICU admission Discharge at 14D	1/20 (5%) vs 25/56 (45%) 0% vs 33%, p=0.093 58% vs 8%, p=0.027
Rosas [473]	Retrospective N=60	Baricitinib, TCZ or combined baricitinib and TCZ. Moderate-severe disease	2/12 deaths on baricitinib monotherapy 4/20 deaths on TCZ monotherapy 3/11 deaths on baricitinib +TCZ	Motality lowest on baracitinib monotherapy. No serious adverse events were observed
Cao [474]	RCT open label, n=43 (22/21)	Ruxolitinib (10mg BD for 14d) WHO stages 4 (most) and 5	Mortality Clinical improvement D14	3 (7.3%) vs 3 (14.3%), p=0.23 21 (51.2%) vs 9 (42.9%), p=0.35
Giudice [475]	Observational, n=17 (7/10)	Ruxolitinib (10mg BD for 14d) and Eculizumab (D7 and D14), hospitalized, severe COVID-19. Combined with GCs, antivirals.	Mortality Progression to ARDS	1/7 vs 1/10 1/7 vs 4/10
Kalil [476]	double-blinded, placebo controlled RCT N=1033	Baricitinib +/- temdesivir WHO stage 4ff	Clinical improvement at D15 Mortality at 28D all Mortality at 28D stage 4 (suppl O2) Mortality at 28D stage 5 (HF or NIV)	OR 1.3 (1.0-1.6) 5.1% vs 7.8% (HR 0.65 (0.39-1.09) 1.9% vs 4.7% (HR 0.4 (0.14-1.14) 7.5% vs 12.9%, HR 0.55 (0.22-1.38)

			Time to recovery WHO stage 3	RR 0.88 (0.63-1.23)
	(515/518)		Time to recovery WHO stage 4	RR 1.17 (0.98-1.39)
			Time to recovery WHO stage 5	RR 1.51 (1.1-2.08)
			Time to recovery MV	RR 1.08 (0.59-1.97)
Marconi [484]	Double blinded, placebo-controlled RCT	Baricitinib 4mg OD for 14d WHO stages 3, 4, 5	28d Mortality overall 28d Mortality WHO stage 4 28d Mortality WHO stage 5	HR 0.57 [0.41-0.78] HR 0.75 [0.45-1.16] HR 0.52 [0.33-0.80]
Guimaraes [291]	Placebo-controlled, open label RCT	Tofacitinib 10mgBD for 14d WHO stage 4, 5 (high flow but no pressure support)	Death or MV day 28 Death 28 d (any cause)	18.1% vs 29% (HR0.63 [0.41-0.97] 2.8% vs 5.5% (HR 0.49 [0.15-1.63]

Table 6. Trials assessing heparin and Aspirin use in COVID-19 (selection)			
Study	**Design, intervention, n**	**Parameters**	**Outcome**
Pavoni [477]	Observational, n=42 WHO stage ≥5ff, high risk group: 90% MV, low risk group: 23% MV	DD≤3000 n=22: ASA, LMWH 4000-6000IU DD≥3000 n=20: ASA, LMWH 50-100IU/kg	LR group: 14% VTE, 4.5% PE; Mortality: 18% HR group: 65% VTE, 10% PE; Mortality: 25%
Chow [478]	Observational retrospective cohort, n=412 WHO stages 4, 5	N=314 no aspirin N=98 aspirin prior to admission Progression to MV Progression to ICU In-hospital mortality	 aHR 0.56, 0.37-0.85, p=0.007 aHR 0.57, 0.38-0.85, p=0.005 aHR 0.53, 0.31-0.90, p=0.02
Yuan [479]	Observational, n=183 (52/131) patients with coronary artery disease (all WHO stages) who were either on ongoing ASA or not	WHO stages 5 (HF O2) 84.6% (ASA), 80.9% (no ASA) 5 (NIV) 19.2% (ASA), 26% (no ASA) 6ff (MV) 1.9% (no ASA), 11.5% (no ASA) All-cause mortality	 OR 0.94 (0.41-2.17), p=0.89
Petito [316]	Observational, Netosis markers in n=36 COVID-19 patients, n=31 healthy controls	Prediction of VTE: MPO-DNA Cit3H	AUC 0.77, p<0.001 AUC 0.79, p<0.001
Hasan [481]	Metanalysis of 12 studies. ICU COVID-19 patients, UFH or LMWH	Prophylactic vs therapeutic anticoagulation of patients with COVID-19 on ICU Pooled prevalence of VTE (all)	 31% (21-43%)

		VTE in prophylactic	38% (10-70%)
		VTE in therapeutic (and prophylactic)	27% (17-40%)
Lu [432]	Metanalysis, 20 observational (VTE incidence) 5 observational (VTE and mortality)	Incidence VTE (pooled, all) Incidence VTE (pooled, ICU) Incidence PE (pooled, all) Incidence PE (pooled ICU) Incidence DVT (pooled, all) Incidence DVT (pooled ICU) Mortality (with/without heparinization n=2886/5647)	255/ 1808, 21% (15-27%) 169/656, 27% (16-38%) 238/1793 15% (10-20%) 148/690 20% (9-31%) 212/1243 27% (19-36%) 99/579 33% (19-47%) RR 0.86 (0.69-1.09)
Birocchi [430]	Metanalysis, 26 studies (17 COVID-19 studies, n=3224; 7 non-COVID-19 studies, n=11.985)	67% COVID-19 on heparin prophylaxis 16% COVID-19 on therapeutic heparin DVT prevalence (pooled) PE (pooled) Non ICU DVT PE ICU patients only DVT PE	15.4% (4.08-31.8%) vs 4.2% (2.3-6.7%) p=0.046 4.9% (0.3-13%) vs 0.2% (0.03-0.6%) p=0.013 2.63%(0.7-5.6%) vs 3.64 (1.9-5.8%) p=0.48 2.83% (1.2-5.1%) vs 0.11 (0.0-0.3), p<0.0001 9.1% (3.6-16.7%) vs 7.4% (6.2-8.7%) p=0.63 11.7% (5.3-20.1) vs 0.96 (0.57-1.5%) p=0.0001 22.2% (5.3-44.6%) vs 6.4% (3.2-10.4%) p=0.48 57% (38-78%) vs 11.5% (6.9-17.6%) p=0.0002
Sridharan [433]	Metanalysis, 11 studies	VTE in hospitalized COVID-19 patients Prophylactic heparin dose Therapeutic heparin dose	12.5% 17.2% OR 0.33 (0.14-0.75), p=0.008

Figure 1.: WHO Ordinal 9 Point Scale and therapeutic options recommended and under investigation during the different disease stages.